

AMENDMENTS TO THE SPECIFICATION

IN THE SPECIFICATION

On page 2, line 13, please replace the original paragraph with the following amended paragraph:

-- Screening of phage display libraries allows rapid identification of peptides binding to a target. However, functional analysis of the phage sequences and their reproduction as soluble and stable peptides are often the most time-consuming parts in the screening. An intein-directed methodology can be used for synthesis and design of peptides obtained by phage display (Björklund *et al.*, 2003). Using this technology, a library of peptide derivatives was made. A novel CTT peptide derivative (CTT2 = GRENYHG-Cyclo-(CTTHWGFTLC)-NH₂) (SEQ ID NO: 1) was identified. It has improved solubility in physiological solutions and is biologically active.--

On page 4, line 3, please replace the original paragraph with the following amended paragraph:

-- **Figure 8.** The biodistribution study of I-125 labelled 6F-Trp CTT2 (GRENYHGCTTH[6-fluoro]WGFTLC)-peptide (SEQ ID NO: 1). The *in vivo* biodistribution of the ¹²⁵I-labeled peptide was assessed at two time points in NMRI/nude mice carrying human ovarian tumours on their lower back. Results are expressed as percentage of injected dose per 1 g tissue (% ID/1g). All values are indicated as mean ± SD of 5 mice.--

On page 5, line 5, please replace the original paragraph with the following amended paragraph:

-- In specific, amidated form of the CTT2 peptide, i.e. GRENYHG-cyclo-(CTTHWGFTLC)-NH₂ (SEQ ID NO: 1), and the new derivatives thereof described herein, i.e. the peptides KRENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2), K(DOTA)RENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2), K(DOTA(In))RENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2), Ac-GRENYHG-cyclo-(CTTHWGFTLC)K-NH₂ (SEQ ID NO: 3), Ac-GRENYHG-cyclo-(CTTHWGFTLC)K(DOTA)-NH₂ (SEQ ID NO: 3), GRENYHG-Cyclo(CTTH(*d,l*-6-Fluoro-W)GFTLC)-NH₂ (SEQ ID NO: 4), GRENYHG-Cyclo(CTTH(*d,l*-5-Fluoro-W)GFTLC)-NH₂ (SEQ ID NO: 4) and GRENYHG-Cyclo-(CTTH(*d,l*-5-OH-W)GFTLC)-NH₂ (SEQ ID NO: 4) are especially suitable for the preparation of the targeting composition.--

On page 5, line 22, please replace the original paragraph with the following amended paragraph:

-- Another object of this invention is a purification method for the targeting composition obtained by covalently attaching the cyclic GRENYHGCTTHWGFTLC peptide (CTT2 peptide) (SEQ ID NO: 1) or a derivative thereof to a synthetic derivative of polyethylene glycol. In the purification method the peptide-lipid mixture obtained is incubated with an organic solvent to obtain a precipitate, the precipitate is centrifuged, washed with an organic solvent and recentrifuged to obtain a pellet, the pellet is suspended into a suitable buffer and size-exclusion chromatography is carried out to obtain pure targeting composition.--

On page 6, line 16, please replace the original paragraph with the following amended paragraph:

--Abbreviations:

AUC	Area Under Curve
CMC	critical micellar concentration
CTT2	amidated cyclic GRENYHGCTTHWGFTLC peptide (SEQ ID NO: 1)
DMF	dimethylformamide
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

Doxil®/Caelyx®	commercially available doxorubicin HCl liposome injection composition by Ortho Biotech, a subsidiary of Johnson & Johnson/Schering Plough Corporation
DSPE-PEG-NHS	1,2-Distearoyl- <i>sn</i> -Glycero-3-Phosphoethanolamine- <i>n</i> -[poly(ethylene glycol)]- <i>N</i> -hydroxysuccinamidyl carbonate
HPLC	high-performance liquid chromatography
MMP	matrix metalloproteinase
PEG	poly(ethylene glycol)
RT	room temperature
SL	stealth liposome
TFA	trifluoroacetic acid
TLC	thin-layer chromatography--

On page 7, line 12, please replace the original paragraph with the following amended paragraph:

-- The pH of dimethylformamide (DMF) (BDH Laboratory Supplies) was adjusted to 8.0 by trifluoroacetic acid (TFA) (Merck). Four milligrams of synthetic amidated GRENYHG-CTTHWGFTLC peptide (CTT2) (SEQ ID NO: 1) (Neosystem S.A.) and 8.6 milligrams of 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*n*-[poly(ethylene glycol)3400]-*N*-hydroxysuccinamidyl carbonate (DSPE-PEG-NHS 3400) (Nektar Corporation) were dissolved in 1 ml DMF (pH 8.0). The mixture (molar ratio 1:1) was incubated at +37°C for two hours with shaking.--

On page 12, line 23, please replace the original paragraph with the following amended paragraph:

-- CTT2 can be viewed as having two structurally distinct parts. Cyclic (-CTTHWGFTLC) part (residues 8-17 of SEQ ID NO: 1) of the peptide is more hydrophobic compared to the linear GRENYHG- part of the peptide (residues 1-7 of SEQ ID NO: 1). The attachment point (N-terminus vs.

C-terminus) of CTT2 peptide to any molecular moiety might have effect on conjugate solubility and bioactivity. Two different peptide derivatives (peptides 1 and 4 in Table 1) were synthesized in order to improve the solubility and bioactivity of conjugates.--

On page 13, line 20, please replace the original paragraph with the following amended paragraph:

-- Indium labelling of DOTA derived peptide: 1.2 mg of K(DOTA)RENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2) was dissolved in 100 µl of ammonium acetate buffer (pH 6.5). InCl₃ was dissolved in ammonium acetate buffer (pH 6.5). Two molar equivalents of InCl₃ solution were added to the peptide solution. Reaction mixture was left standing overnight at RT. Indium-labelled peptide was purified by reverse phase C-18 cartridges using ammonium acetate buffer (pH 6.5) and acetonitrile solution (50%/50%). Indium-labelled peptides were obtained as white solid after lyophilization of freezed eluates. Indium-labelled peptides were identified by MALDI-TOF MS.--

On page 14, line 1, please replace the original paragraph with the following amended paragraph:

-- **Table 1:** Derivatives of CTT2 peptide (see Figures 7b to 7i for the molecular structures)

Peptide sequence	Exact mass (M)/g/mol	Observed mass (M+H ⁺)/g/mol
(1) KRENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2)	2049,89	2050,91
(2) K(DOTA)RENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2)	2436,07	2436,99
(3) K(DOTA(In))RENYHG-cyclo-(CTTHWGFTLC) (SEQ ID NO: 2)	2547,95	2548,69
(4) Ac-GRENYHG-cyclo-(CTTHWGFTLC)K-NH ₂ (SEQ ID NO: 3)		

(5) Ac-GRENYHG-cyclo-(CTTHWGFTLC)K(DOTA)-NH ₂ (SEQ ID NO: 3)		
(6) GRENYHG-Cyclo(CTTH(<i>d,l</i> -6-Fluoro-W)GFTLC)-NH ₂ (SEQ ID NO: 4)	1995,83	1996,77
(7) GRENYHG-Cyclo(CTTH(<i>d,l</i> -5-Fluoro-W)GFTLC)-NH ₂ (SEQ ID NO: 4)	1995,83	
(8) GRENYHG-Cyclo(CTTH(<i>d,l</i> -5-OH-W)GFTLC)-NH ₂ (SEQ ID NO: 4)	1995,83	

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AMENDMENTS TO THE SEQUENCE LISTING

IN THE SEQUENCE LISTING

Please replace the Sequence Listing of record with the Substitute Sequence Listing enclosed herewith.